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EDITORIAL

Beyond Neuroprotection to Brain Repair: Exploring the Next Frontier in Clinical Neuroscience to Expand the Therapeutic Window for Stroke

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Stroke is the number one cause of disability in the USA; despite remarkable advancements in the primary and secondary prevention of stroke, over five million Americans (and many more of our brethren around the world) possess significant limitations in their ability to lead a quality life as a result of stroke [1]. Patients of mine who expected to retire to lives of playing golf and chasing their grandchildren instead are often relegated to a sedentary and more isolated existence. These clinical examples represent only the tip of the iceberg of the handicap and suffering that develops too often following stroke. It is thus surprising that unlike the treatment of cancer, so few clinical trials related specifically to stroke recovery are available for our patients.

The lack of clinical trials related to stroke recovery is contrasted with an awesome explosion in our understanding of cell death pathways, axonal regeneration, stem cells, remyelination, and synaptogenesis. Pioneering work of Randy Nudo and colleagues has been expanded on by a number of stroke recovery biologists including Tim Murphy, Michael Chopp, Eng Lo, and Tom Carmichael who continue to leverage the best in contemporary neuroscience to shed light on the biology of post-acute stroke [2–6]. How can we change the current translational trajectory to begin to harness remarkable advances in our understanding of the biology of stroke injury and repair to appropriate pharmacological and biological manipulations in animals and then in humans?

First, we must begin to educate the medical and lay communities regarding the urgency surrounding the growing epidemic of brain disability following ischemic or hemorrhagic stroke. A project mentality, much like that surrounding the Manhattan Project, must be developed. One of the *first mandates* of this project must be to rigorously define the natural history of ischemic and hemorrhagic stroke so that we can appropriately counsel those patients who are likely to lead lives of long-term disability to participate in clinical trials. It would be ideal to have blood and imaging biomarkers that facilitate prospective identification of those patients who are likely to do poorly [7].

The *second mandate* of this project will be to develop rodent models of stroke recovery that appropriately reflect the challenges faced by humans. While the primate models of stroke have created enormous intellectual momentum, widely utilized rodent models of stroke often target behaviors that spontaneously recover. And although altering the kinetics of recovery is a tangible goal with medical and financial benefits, it does not allow the identification of therapeutic approaches that change the amplitude of recovery [8]. As many stroke patients experience little to no improvement in some functions, being able to model persistent deficits in physiologically meaningful paradigms (e.g., permanent and transient ischemia) is essential.

A *third mandate* of this project relates directly to mandate 2. Specifically, with the animal models, we need to harness the enormous expertise that exists in behavioral neuroscience community that historically has been used to study learning and memory to monitor rodent behavior in ways that allow us to define the critical biological parameters required to restore impairments such as vision, hand movement, and speech [9]. An untested set of assumptions are that growing axons longer, increasing neurogenesis and increasing angiogenesis, are primary goals in achieving recovery.

The *fourth mandate* of this project must be to create infrastructures for the development of small molecule "sets"

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that are structurally diverse but whose commonality is to affect a single target. For example, a set of small molecules that activate or inhibit the BDNF receptor, TrkB, would allow one to ask whether this is a viable target for manipulation following stroke. Genetic knockouts are valuable in defining the selectivity of drugs for targets, but it is often difficult to manipulate these targets using molecular tools post-injury in a way that is clinically meaningful. Medicinal chemists must partner with stroke biologist to facilitate rapid evaluation of the most promising targets [10].

The *fifth mandate* of this project must be to create an understanding of how the acute injury process interfaces with brain repair and vice versa. We now know from many studies now that starting rehabilitation too early may be detrimental likely due to extant worsening of glutamate dyshomeostasis after stroke [11]. It is thus important to develop repair approaches that protect the brain. We have dual developed several molecules that have the ability to not only enhance repair but also to protect neurons. Effective agents which posses protective and repair capacities will have at least three important benefits: (1) they can be used at any time after the initial ictus for protection or repair and thus have a wide therapeutic window; (2) they allow one to consider starting a repair agent very early without concern that it might damage the brain; and (3) when used as neuroprotective agents, they provide assurance that neuroprotection will not foul the landscape for repair. Along these lines, members of our Institute have identified three viable targets to meet these lofty challenges in vitro but are just making their way to stroke models: (1) *Inducers of arginase 1 transcription*—These have the ability induce a cassette of genes, including arginase 1 that can reduce nitric oxide toxicity (by degrading arginine), and also overcome barriers to regeneration by converting arginine to polyamines [12]. The prototype of this group is the soy isoflavone daidzein [10]. (2) *Inhibitors of the Hypoxia inducible factor prolyl hydroxylases*—Inhibitors of these enzymes have the ability to activate 70 to 100 genes involved in adaptation to ischemia, including erythropoietin, vascular endothelial growth factor, and heme-oxgygenase that cannot only protect the brain but also enhance neurogenesis and angiogenesis. HIF PHD inhibition appears to convert or divert the prodeath effects of HIF activation toward survival [13]. The prototype of this group is the iron chelator, desferoxamine. (3) *Isoform selective HDAC6 inhibitors*—Brett Langley and colleagues at Burke and Cornell showed that selective inhibitors of HDAC6 not only have the ability to protect the brain but also enhance the growth of axons in the presence of myelin inhibitors or chondroitin sulfate proteoglycans. The prototype of this group of compounds is tubastatin [14]. Testing of compounds selective for each of these targets according to the well-developed STAIR criteria is essential.

Any good project of this magnitude and impact requires a pluralistic effort from investigators representing diverse fields from around the world. The mandates enumerated in this Editorial represent only a beginning, and a central mission of this journal, *Translational Stroke*, is, among other things, to catalyze consortium-driven efforts that can move beyond incremental improvements to change therapeutics. I finish by respectfully challenging my colleagues to join with me to build on these mandates to expand stroke therapeutics to all patients, not simply the few that make it to the hospital within 3 h of the onset of their ischemia.

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